Meta-Analysis of Impact of Anemia and Hemoglobin Level on Survival After Transcatheter Aortic Valve Implantation

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To establish evidence whether baseline anemia and decreases in baseline hemoglobin levels affect survival after transcatheter aortic valve implantation (TAVI), we performed a meta-analysis of available studies. Studies considered for inclusion met the following criteria: the design was a comparative study of patients with baseline anemia versus those without baseline anemia or a cohort study investigating baseline anemia (as a dichotomous variable) or baseline hemoglobin levels (as a continuous variable) as one of prognostic factors of mortality; the study population was patients who underwent TAVI; and main outcomes included early (30-day or in-hospital) or late (including early) all-cause mortality. Study-specific estimates were combined in the random-effects model. Our search identified 15 eligible studies including a total of 11,657 TAVI patients. Pooled analysis demonstrated that baseline anemia was associated with a statistically significant increase in early ($p = 0.003$) and midterm mortality ($p < 0.0001$) and that incremental decreases in baseline hemoglobin levels were associated with a statistically significant increase in midterm mortality ($p < 0.00001$). Pooled analysis of only adjusted estimates indicated that anemia was independently associated with a statistically significant increase in early ($p = 0.02$) and midterm mortality ($p < 0.0001$) and that incremental decreases in baseline hemoglobin levels were independently associated with a statistically significant increase in midterm mortality ($p < 0.00001$). In conclusion, baseline anemia and lower baseline hemoglobin levels may be associated with increased early and midterm mortality after TAVI. **(Am J Cardiol 2019;123:306−314)**

Baseline anemia is associated with increased early mortality, acute kidney injury, and infection after surgery and with increased early mortality also after cardiac surgery.[1]

Anemia in percutaneous coronary intervention (PCI) is independently associated with twofold increased mortality, major adverse cardiovascular events (MACE), and major bleeding, with risk elevation related to incremental decreases in hemoglobin levels.[2] Because blood transfusion is more frequent in patients with anemia, diagnosis of anemia may change clinical practice in surgery and intervention. Blood transfusion also is independently associated with threefold increased mortality and MACE after PCI with dose-dependent adverse influence on mortality.[3] Although several studies reported impact of baseline anemia and hemoglobin levels on survival after transcatheter aortic valve implantation (TAVI) for patients with severe aortic stenosis, no meta-analysis of them has been conducted to date. In the present article, to establish evidence whether baseline anemia and decreases in baseline hemoglobin levels affect survival after TAVI, we performed a meta-analysis of available studies.

Methods

All studies investigating impact of anemia and hemoglobin levels on survival after TAVI were identified using a 2-level search strategy. First, databases including MEDLINE and EMBASE were searched through June 2018 using Web-based search engines (PubMed, OVID). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis. Search terms included *anemia*, *anaemia*, *anemic*, *anaemic*, *hemoglobin*, *haemoglobin*, *hematocrit*, or *haematocrit*; *percutaneous*, *transcatheter*, *transluminal*, *transarterial*, *transapical*, *transaortic*, *transcarotid*, *transaxillary*, *trans-subclavian*, *trans-subclavian*, *transiliac*, *transfemoral*, *transiliofemoral*, or *transcaval*; *aortic valve*; and *implantation* or *replacement*.

Studies considered for inclusion met the following criteria: the design was a comparative study of patients with baseline anemia versus those without baseline

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anemia or a cohort study investigating baseline anemia (as a dichotomous variable) or baseline hemoglobin levels (as a continuous variable) as one of prognostic factors of mortality; the study population was patients who underwent TAVI; and main outcomes included early (30-day or in-hospital) or late (including early) all-cause mortality. Data regarding detailed inclusion criteria, definition of anemia, duration of follow-up, and early and/or late mortality were extracted (as available) from each individual study.

For each study, data regarding mortality in both the anemia and nonanemia groups were used to generate odds ratios (ORs) and 95% confidence intervals. Otherwise, ORs and hazard ratios (HRs) for mortality (preferentially adjusted, not but unadjusted, estimates) reported in individual studies were directly extracted, or HRs were calculated from Kaplan-Meier curve data or summary data using the HR-calculations spreadsheet provided by Tierney et al[4] based on statistical methods reported by Parmar et al[5] and Williamson et al.[6] Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs/HRs in the random-effects model. Publication bias was assessed graphically using a funnel plot and mathematically using the linear-regression test. All analyses were conducted using Review Manager version 5.3 (available from http://tech.cochrane.org/revman) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ).

Results

Our search identified 15 eligible studies[7–21] enrolling a total of 11,657 TAVI patients. Patient, echocardiographic, and procedural characteristics are summarized in Table 1 and Supplementary Table S1. There were 7 comparative studies[7–13] of patients with baseline anemia versus those without baseline anemia and 8 cohort studies[14–21] investigating baseline anemia (dichotomous variable)[15,18] or baseline hemoglobin levels (continuous variable)[14,16–21] as one of prognostic factors of mortality. Anemia was defined as hemoglobin levels <13 g/dl in men and <12 g/dl in women according to the definition of the WHO (World Health Organization) in all the 7 comparative studies,[7–13] <10 g/dl in a cohort study,[15] and <12.5 g/dl in another cohort study.[18] In a comparative study,[7] patients with anemia were classified into tertiles of mild (12.0 to 12.99 g/dl in men, 11.30 to 11.99 g/dl in women), moderate (10.80 to 11.99 g/dl in men, 10.23 to 11.29 g/dl in women), and severe anemia (<10.80 g/dl in men; <10.23 g/dl in women), and furthermore all patients were divided into 3 (no/mild, moderate, and severe anemia) groups. We combined the moderate and severe anemia groups, and considered the combined group as an anemia group. For anemia (as a dichotomous variable), adjusted ORs/HRs of early mortality could be extracted from 3 studies,[9,10,12] and those of midterm mortality from 6 studies[7,10,12,13,15,18] (Table 2). For hemoglobin levels (as a continuous variable), adjusted HRs of midterm mortality could be extracted from 6 studies[10,16,17,19–21] (Table 3), and only 2 HRs of early mortality,[10,17] which we did not combine in a meta-analysis, was available.

Pooled analysis demonstrated that baseline anemia was associated with a statistically significant increase in early (Figure 1) and midterm (1 to 3 year) mortality (Figure 2) and that incremental decreases in baseline hemoglobin levels were associated with a statistically significant increase in midterm (1 to 2 year) mortality (Figure 3). Pooled analysis of only adjusted estimates indicated that anemia was independently associated with a statistically significant increase in early (Figure 4) and midterm mortality (Figure 5) and that incremental decreases in baseline hemoglobin levels were independently associated with a statistically significant increase in midterm mortality (Figure 6).

To assess publication bias, we generated a funnel plot of the logarithm of effect size (OR/HR) versus the precision (reciprocal of standard error) for each study. There was no statistically significant funnel-plot asymmetry (suggesting publication bias) in anemia for early ($p = 0.89$; Figure 7) and midterm mortality ($p = 0.16$; Figure 8) and in hemoglobin levels for midterm mortality ($p = 0.06$; Figure 9).

Discussion

Results of the present analysis suggest that baseline anemia and lower baseline hemoglobin levels may be associated with increased early and midterm mortality after TAVI. In general, baseline anemia is a predictor of worse outcomes after cardiac surgery and intervention. A meta-analysis[1] showed an association of anemia with increased early (in-hospital/30-day) mortality after cardiac surgery. In another meta-analysis,[2] anemia predicted increased post-PCI (from in-hospital up to 4.5-year) mortality and MACE. Incremental decreases in hemoglobin and hematocrit levels were also associated with worse mortality.[2] These findings may strengthen the present results. In patients who underwent TAVI who are older and considered to be high risk for surgery because of multiple comorbidities, the etiology of anemia is multifactorial, that is due to nutritional (e.g. iron, vitamin B12, and folate) deficiency, the presence of chronic (e.g. diabetes and renal failure) and inflammatory diseases (e.g. rheumatoid arthritis), and any myelodysplastic syndrome as well as occult bleeding from the gastrointestinal tract,[13,22–24] which may partially explain worse survival after TAVI with baseline anemia.

Baseline anemia is associated with increased incidence of transfusion after TAVI,[7,8,10–13] and transfusion per se may independently predict increased 30-day[17] and midterm[25–27] mortality after TAVI. Meanwhile, baseline anemia per se may be associated with increased mortality after TAVI independently of transfusion as well as other covariates. In the present analysis of only adjusted estimates, anemia independently predicted increased early (Figure 4) and midterm mortality (Figure 5).

Despite not addressing in the present analysis, not only baseline but also postprocedural anemia may be associated with increased mortality after TAVI. Arai et al[7] reported an association of increased severity

Table 1
Patient characteristics

Comparative study

Study	Reference	Patient number			Anemia (%)		Hb (g/dl)		Age (years)			Men (%)		
		Total	Anemia	Nonanemia	Definition		Anemia	Nonanemia	Anemia	Nonanemia	p	Anemia	Nonanemia	p
Arai (FRANCE 2) 2015	7	3472	1335	2137	WHO*	38.5	10.4	13.1	82.4	82.7	N/A	54.0	49.0	N/A
DeLarochellière 2015	8	438	282	156	WHO†	64.4	10.8±1.1	13.4 ±1.0	80±8	78±9	0.020	51.8	43.6	0.101
Hellhammer 2016	9	376	239	137	WHO†	63.6	11.0±1.1	13.6±1.1	82±6.2	81±5.9	0.101	46.9	40.1	0.207
Nuis 2013	10	1696	969	727	WHO†	57.1	11.0±1.1	13.6±1.0	81±7	80±7	0.001	55.8	47.2	< 0.001
Rheude 2017	11	549	249	300	WHO†	45.4	11.0±1.1	13.8±1.1	82±6	80±6	< 0.001	54.6	54.3	0.947
Seiffert 2017	12	1201	707	491	WHO†	58.9	N/A		82.1 (76.4−85.6)	81.9 (76.9−85.3)	0.854	53.3	41.3	< 0.001
Van Mieghem 2011	13	118	58	60	WHO†	49.2	10.8±1.1	13.4±1.1	82 (78−86)	82 (78−86)	0.85	39.7	46.7	0.44

Cohort study

Study	Reference	Patient number	Anemia (%)		Hb (g/dl)	Age (years)	Men (%)
Collas 2016	14	197	N/A		12.2±1.4	82 (77−86)	46.2
Debonnaire 2015	15	511	Hb < 10 g/dl	N/A	12.1±1.6	82 (77-86)	38.0
Duckheim 2017	16	374	N/A		12.3±1.58	82.3±6.5	49.7
Escárcega 2015	17	332	N/A		11.4	82	51.2
Gotzmann 2013	18	202	Hg < 12.5 g/dl	N/A	12.5±1.6	79±6	47.0
ITER (Salizzoni) 2016	19	1904	N/A		11.8±1.6	81.7±6.2	39.8
Seiffert 2014	20	845	N/A		11.9±1.7	80.9±6.5	48.9
TOPAS-TAVI (Ribeiro) 2018	21	287	N/A		11.9±1.7	80±7	72.1

FRANCE = French Aortic National CoreValve and Edwards; Hb = hemoglobin; ITER = Italian Transcatheter Balloon-Expandable Valve Implantation Registry; N/A = not available; TOPAS-TAVI = true or pseudo-severe aortic stenosis-transcatheter aortic valve implantation; WHO = World Health Organization.

Continuous variables are expressed as number, percent, mean, mean ± standard deviation, or median (interquartile range).

* Hb levels < 12.00 g/dl in men and < 11.30 g/dl in women (excluding "mild" anemia).

† Hb levels < 13 g/dl in men and < 12 g/dl in women.

Table 2
Odds and hazard ratio (OR and HR) of mortality for anemia

Study	Reference	Early mortality		Late mortality	
		Flow-up	Point estimate [95% confidence interval]	Flow-up	Point estimate [95% confidence interval]
Arai (FRANCE 2) 2015	7	30 days	Unadjusted OR, 1.41 [1.08, 1.84]	1 year	Adjusted HR, 1.44 [1.28, 1.63]
Debonnaire 2015	15	N/A		1 year	Adjusted HR, 2.03 [1.11, 3.73]
DeLarochellière 2015	8	30 days	Unadjusted OR, 0.77 [0.36, 1.66]	1 year	Unadjusted HR, 1.14 [0.69, 1.89]
Gotzmann 2013	18	N/A		1.5±0.9 years	Adjusted HR, 3.62 [2.025, 6.468]
Hellhammer 2016	9	30 days	Adjusted OR, 2.10 [0.70, 6.29]	N/A	
Nuis 2013	10	30 days	Adjusted HR, 1.732 [0.96, 3.12]	1 year	Adjusted HR, 1.42 [1.12, 1.81]
Rheude 2017	11	In hospital	Unadjusted OR, 1.82 [0.30, 10.96]	1 year	Unadjusted OR, 5.29 [2.49, 11.23]
Seiffert 2017	12	30 days	Adjusted HR, 1.60 [0.43, 5.99]	3 years	Adjusted HR, 1.13 [0.79, 1.61]
Van Mieghem 2011	13	30 days	Unadjusted OR, 0.87 [0.28, 2.77]	1 year	Adjusted HR, 2.10 [1.06, 4.18]
Total	–	–	***1.39 [1.12, 1.72]*** (Figure 1)	–	***1.74 [1.35, 2.25]*** (Figure 2)
Total, adjusted only	–	–	***1.78 [1.10, 2.88]*** (Figure 4)	–	***1.62 [1.29, 4.18]*** (Figure 5)

FRANCE = French Aortic National CoreValve and Edwards; N/A = not available.

Table 3
Hazard ratio (HR) of mortality per 1-g/dl decrease in hemoglobin levels

Study	Reference	Early mortality		Late mortality	
		Flow-up	Point estimate [95% confidence interval]	Flow-up	Point estimate [95% confidence interval]
Collas 2016	14	N/A		1 year	Unadjusted HR, 1.32 [1.03, 1.68]*
Duckheim 2017	16	N/A		1 year	Adjusted HR, 1.24 [1.04, 1.47]*
Escárcega 2015	17	30 days	Unadjusted HR, 0.95 [0.70, 1.28]*	1 year	Adjusted HR, 1.12 [0.94, 1.33]*
Gotzmann 2013	18	N/A		1.5±0.9 years	Unadjusted HR, 1.47 [1.238, 1.742]*
ITER (Salizzoni) 2016	19	N/A		Median, 2.1 years	Adjusted HR, 1.11 [1.02, 1.20]*
Nuis 2013	10	30 days	Adjusted HR, 1.11 [0.95, 1.30]*	1 year	Adjusted HR, 1.14, 1.06, 1.23]*
Seiffert 2014	20	N/A		1 year	Adjusted HR, 1.15 [1.05, 1.27]*
TOPAS-TAVI (Ribeiro) 2018	21	N/A		2 years	Adjusted HR, 1.27 [1.11, 1.45]
Total	–	–	***Not performed***	–	***1.19 [1.12, 1.26]*** (Figure 3)
Total, adjusted only	–	–	***Not performed***	–	***1.15 [1.10, 1.20]*** (Figure 6)

ITER = Italian Transcatheter Balloon-Expandable Valve Implantation Registry; N/A = not available; TOPAS-TAVI = True or Pseudo-severe Aortic Stenosis-Transcatheter Aortic Valve Implantation.
* Calculated using unadjusted/adjusted HR of mortality per 1-g/dl increase in hemoglobin levels.

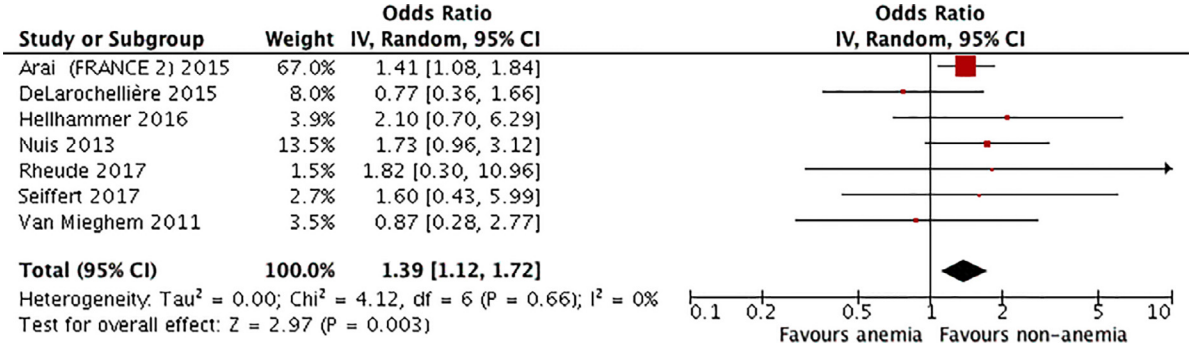

Figure 1. Forest plot of odds and hazard ratios of early mortality for baseline anemia. CI = confidence interval; FRANCE = French Aortic National CoreValve and Edwards; IV = inverse variance.

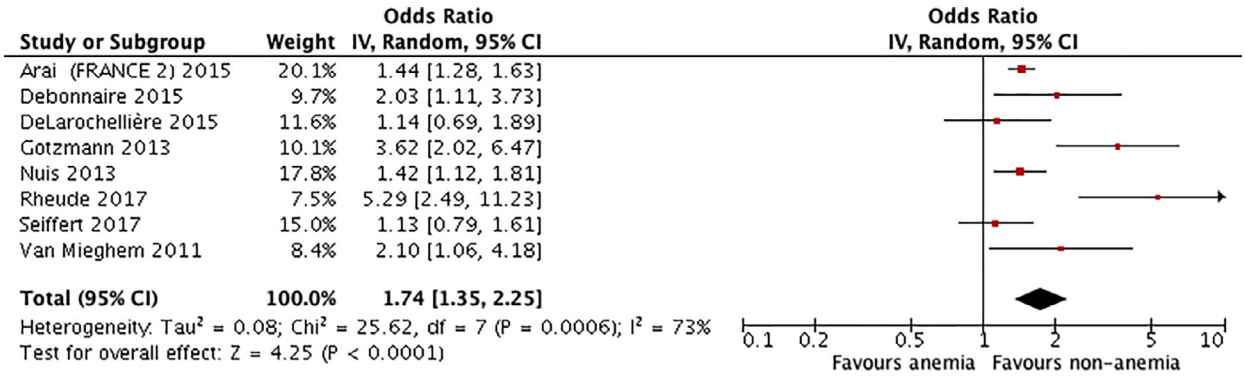

Figure 2. Forest plot of odds and hazard ratios of midterm mortality for baseline anemia. CI = confidence interval; FRANCE = French Aortic National CoreValve and Edwards; IV = inverse variance.

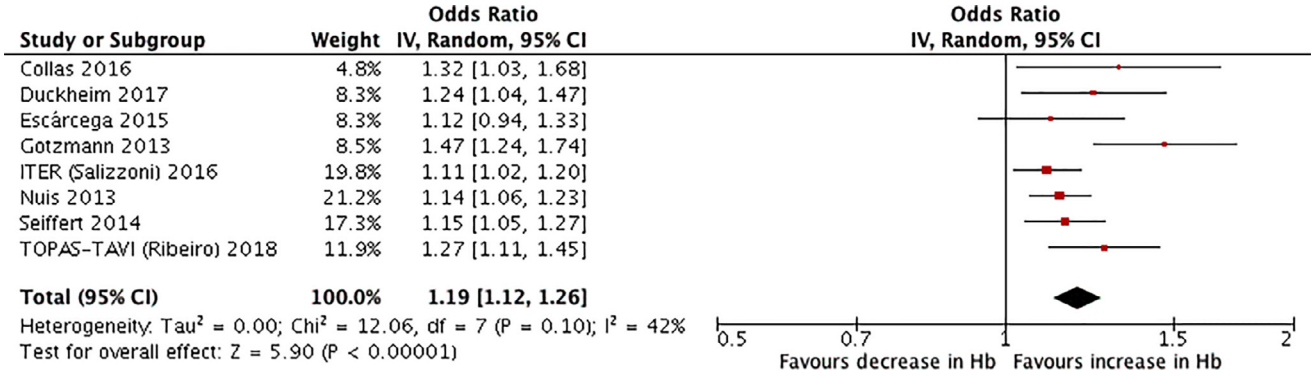

Figure 3. Forest plot of hazard ratios of midterm mortality per 1-g/dl decrease in baseline hemoglobin levels. CI = confidence interval; ITER = Italian Transcatheter Balloon-Expandable Valve Implantation Registry; IV = inverse variance; TOPAS-TAVI = True or Pseudo-severe Aortic Stenosis-Transcatheter Aortic Valve Implantation.

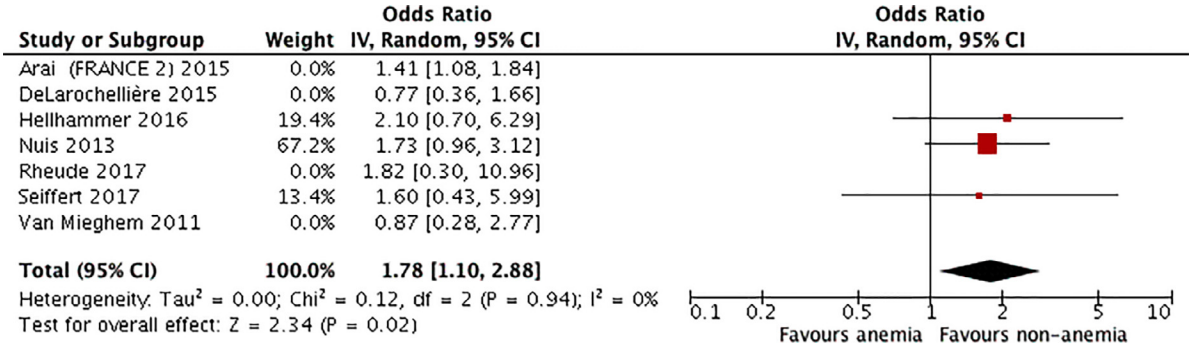

Figure 4. Forest plot of adjusted odds and hazard ratios of early mortality for baseline anemia. CI = confidence interval; FRANCE = French Aortic National CoreValve and Edwards; IV = inverse variance.

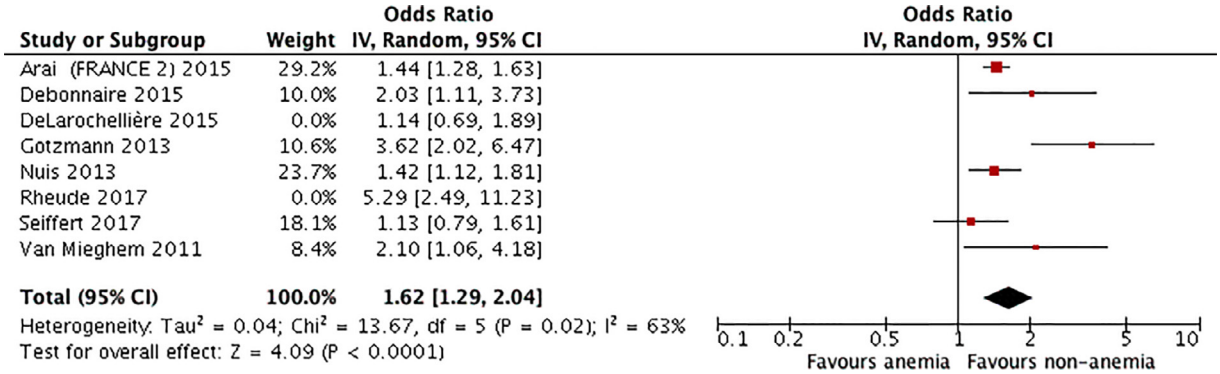

Figure 5. Forest plot of adjusted hazard ratios of midterm mortality for baseline anemia. CI = confidence interval; FRANCE = French Aortic National CoreValve and Edwards; IV = inverse variance.

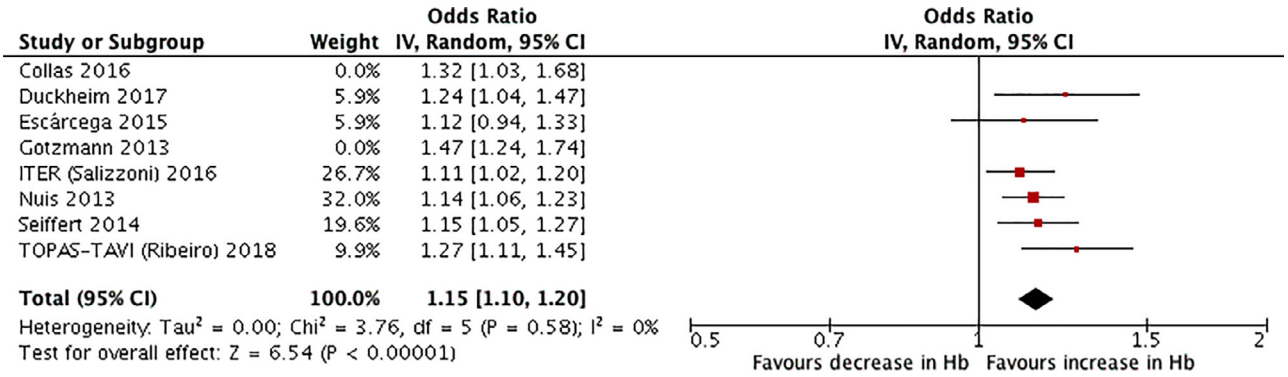

Figure 6. Forest plot of adjusted hazard ratios of midterm mortality per 1-g/dl decrease in baseline hemoglobin levels. CI = confidence interval; ITER = Italian transcatheter balloon-expandable valve implantation registry; IV = inverse variance; TOPAS-TAVI = true or pseudo-severe aortic stenosis-transcatheter aortic valve implantation.

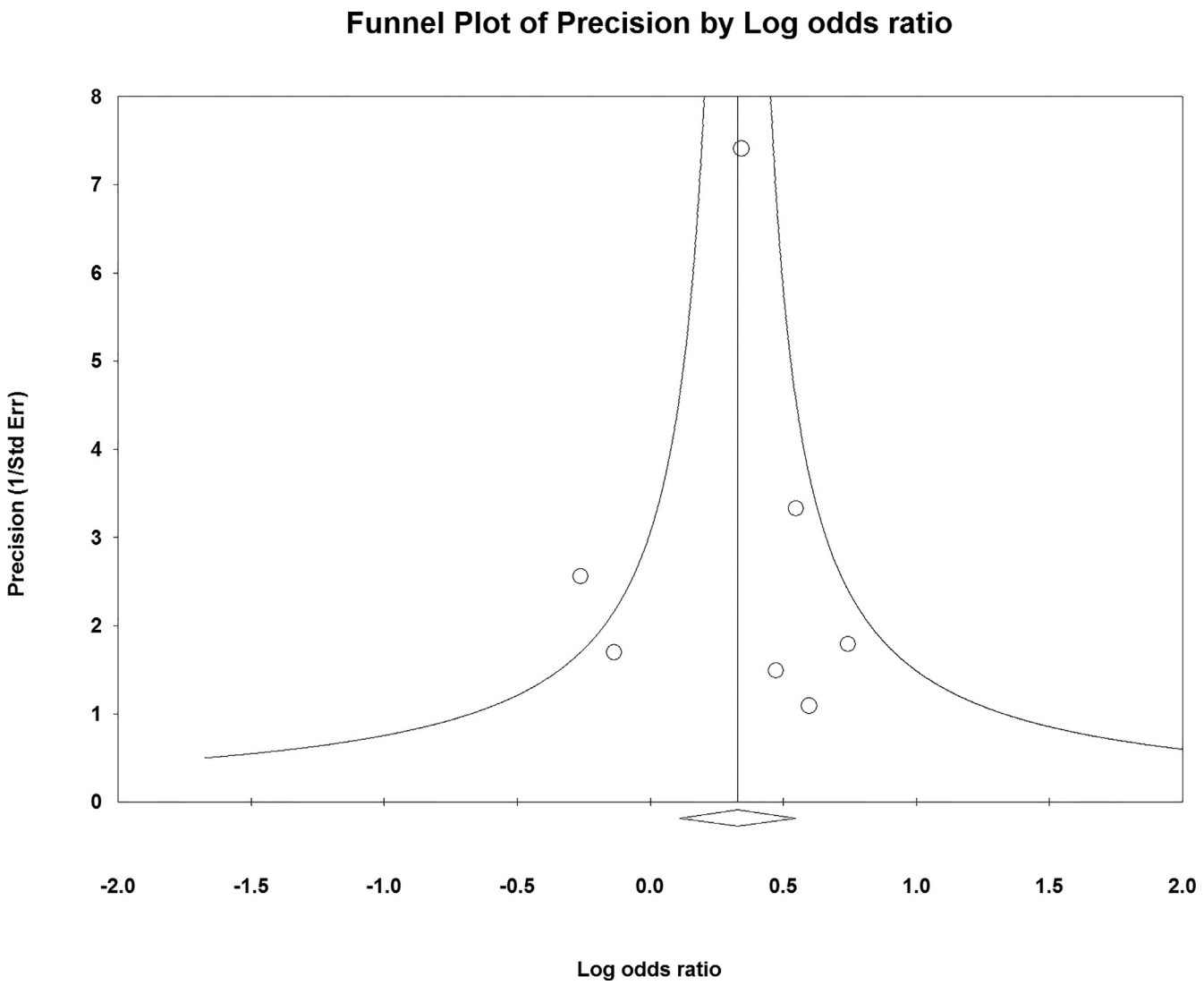

Figure 7. Funnel plot of odds and hazard ratios of early mortality for baseline anemia.

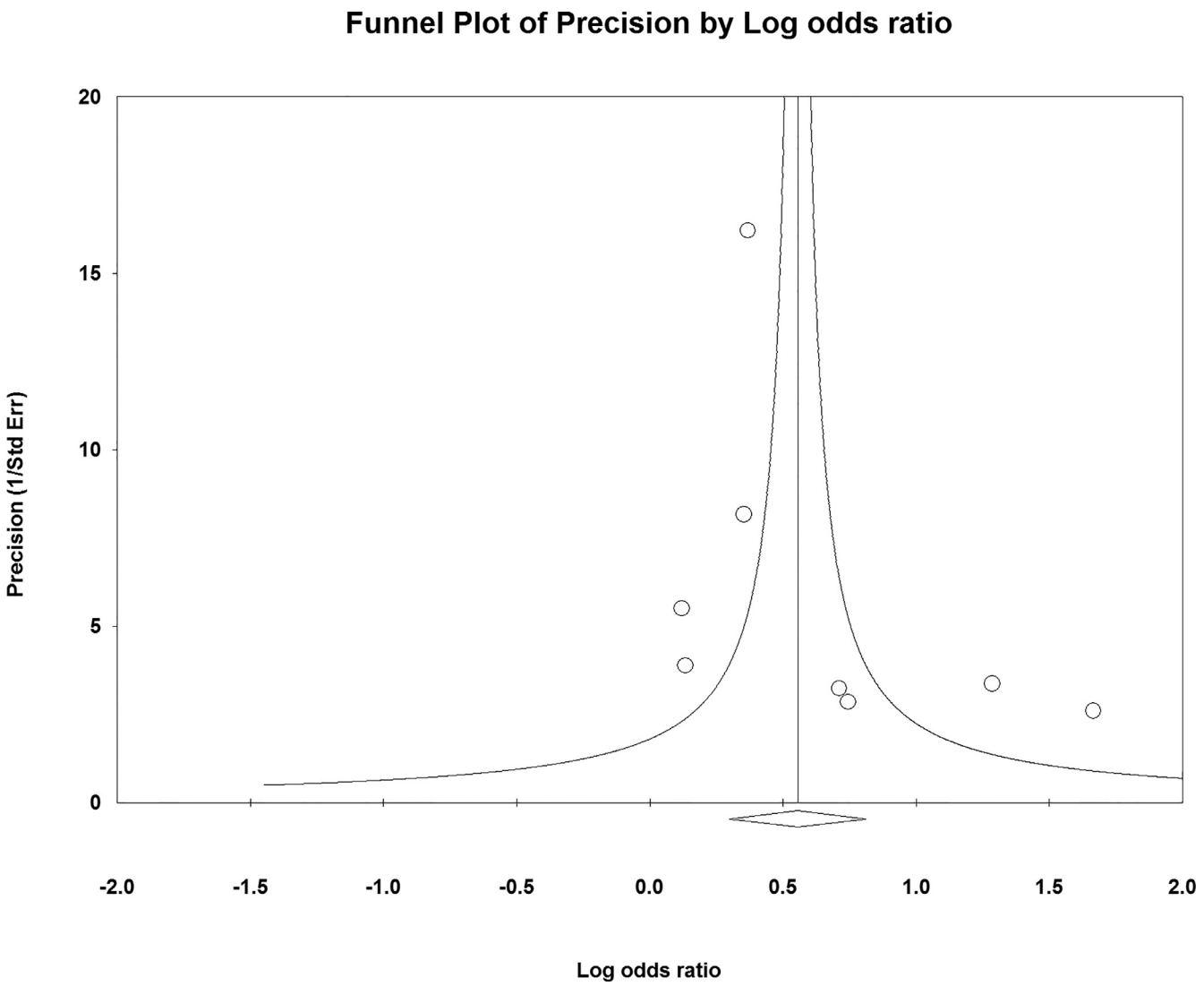

Figure 8. Funnel plot of odds and hazard ratios of midterm mortality for baseline anemia.

(<2 g/dl, 2 to 4 g/dl, and >4 g/dl) in postprocedural hemoglobin drop with differences in 30-day (5.9%, 6.0%, and 11.8%, respectively; $p < 0.01$) and 1-year mortality (16%, 18%, and 23%, respectively; $p < 0.01$). Postprocedural hemoglobin drop was also a predictor of increased 1-year mortality independently of potential confounders including baseline anemia.[7] In the study by Konigstein et al,[27] ≥3 g/dl hemoglobin drop predicted increased long-term (>3 year) mortality independently of potential confounders including transfusion. Furthermore, in patients with <3 g/dl hemoglobin drop, transfusion was associated with increased long-term mortality; there was no difference in mortality between ≥3 g/dl hemoglobin drop without transfusion and <3 g/dl hemoglobin drop with/without transfusion; and, in patients with ≥3 g/dl hemoglobin drop, transfusion was associated with increased mortality. For the same hemoglobin drop, transfusion may be a predictor of increased long-term mortality.

We must interpret the present results with caution in the context of limitations. First, anemia may be one of surrogate markers of greater comorbidity and frailty in patients who underwent TAVI, and inadequately adjusting for confounders such as comorbidity and frailty burden may influence statistical results.[2] Our pooled analysis of only adjusted estimates, however, did not substantially alter the results favoring baseline nonanemia and higher baseline hemoglobin levels. Second, publication bias unfavorable for baseline anemia and lower baseline hemoglobin levels may influence the present results. Exhaustively searching the available literature, however, minimized this risk, and the established statistical test did not detect such bias. Third, the definitions of anemia were a little heterogeneous. It is considered, however, that the heterogeneity may not substantively change the results of our analysis.

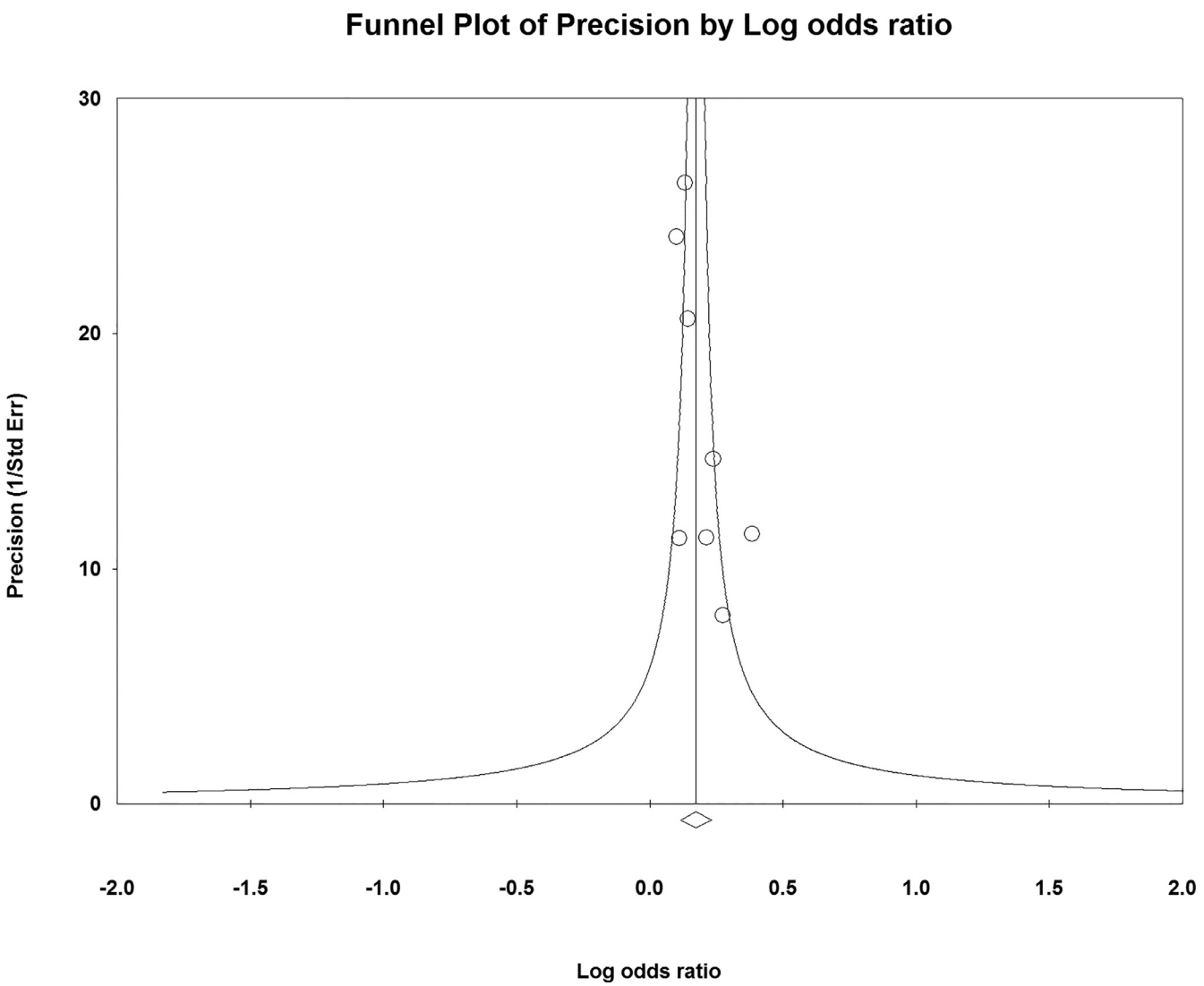

Figure 9. Funnel plot of hazard ratios of midterm mortality per 1-g/dl decrease in baseline hemoglobin levels.

In conclusion, baseline anemia and lower baseline hemoglobin levels may be associated with increased early and midterm mortality after TAVI.

Disclosures

The investigators have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.09.042.

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